

WE CLAIM:

1. A method of reducing the damage done by reactive oxygen species (ROS) in an animal comprising administering to the animal an effective amount of a peptide having the formula:

$$P_1 - P_2,$$

wherein:

P_1 is:

$Xaa_1 Xaa_2 His$: or

$Xaa_1 Xaa_2 His Xaa_3$;

P_2 is $(Xaa_4)_n$;

Xaa_1 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_2 is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_3 is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa_4 is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

2. The method of Claim 1 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

3. The method of Claim 1 wherein Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

4. The method of Claim 1 wherein Xaa_3 is lysine.

5. The method of Claim 1 wherein Xaa_1 is aspartic acid, glutamic acid, arginine,

threonine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

6. The method of Claim 5 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

7. The method of Claim 6 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

8. The method of Claim 7 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

9. The method of Claim 1 wherein n is 0-10.

10. The method of Claim 9 wherein n is 0-5.

11. The method of Claim 10 wherein n is 0.

12. The method of Claim 1 wherein P₂ comprises a metal-binding sequence.

13. The method of Claim 12 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

14. The method of Claim 13 wherein Xaa₅ is Orn or Lys.

15. The method of Claim 12 wherein P₂ comprises one of the following sequences:

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

[(Xaa₄)_mXaa₅Xaa₂His]_r,

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃(Xaa₄)_mXaa₅Xaa₂His]_r, or

[(Xaa₄)_mXaa₅Xaa₂His(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂, m is 0-5 and r is 2-100.

16. The method of Claim 12 wherein P₂ comprises a sequence which binds Cu(I).

17. The method of Claim 16 wherein P₂ comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,
 Cys Cys,
 Cys Xaa₄ Cys,
 Cys Xaa₄ Xaa₄ Cys,
 Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,
 Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],
 Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],
 Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or
 γ-Glu Cys Gly.

18. The method of Claim 17 wherein P₂ is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

19. The method of Claim 1 wherein P₂ comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

20. The method of Claim 19 wherein P₂ is hydrophobic or an arginine oligomer.

21. The method of Claim 1 wherein at least one of the amino acids of P₁ other than β-alanine, when present, is a D-amino acid.

22. The method of Claim 21 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids.

23. The method of Claim 22 wherein all of the amino acids of P₁ other than β-alanine, when present, are D-amino acids.

24. The method of Claim 21 wherein at least 50% of the amino acids of P₂ are D-amino acids.

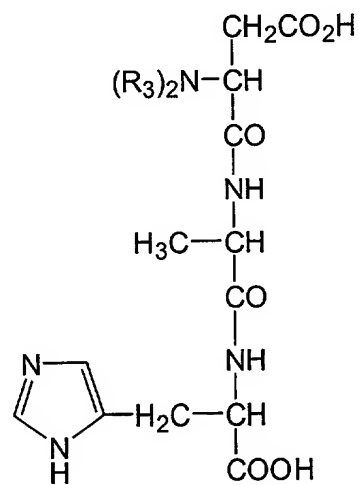
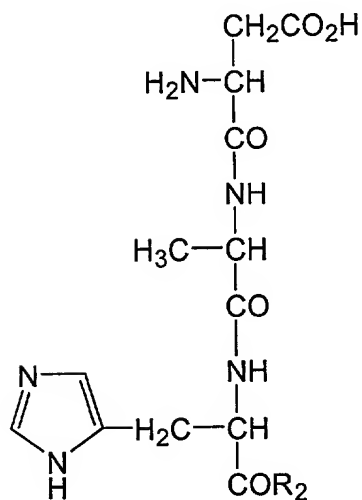
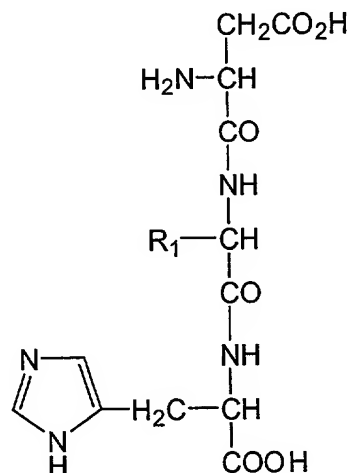
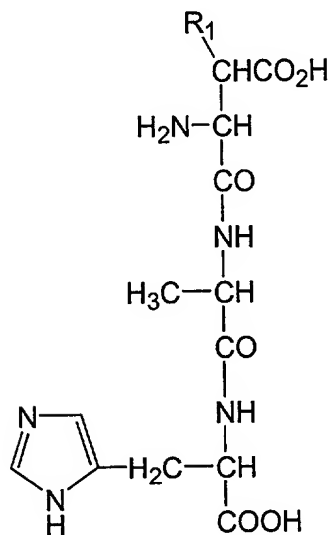
25. The method of Claim 22 wherein at least 50% of the amino acids of P₂ are D-amino acids.

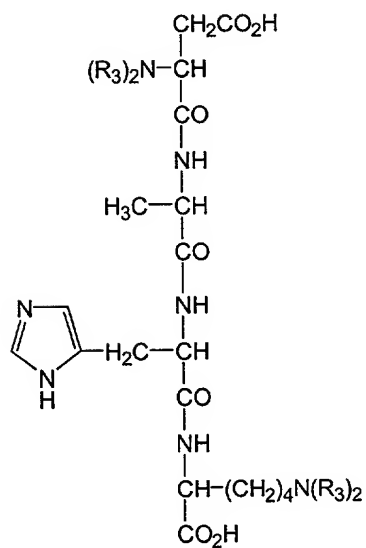
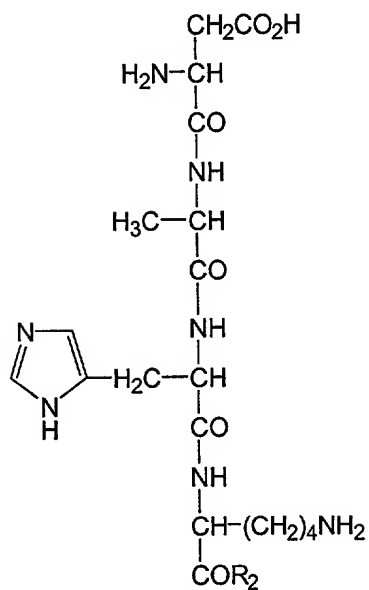
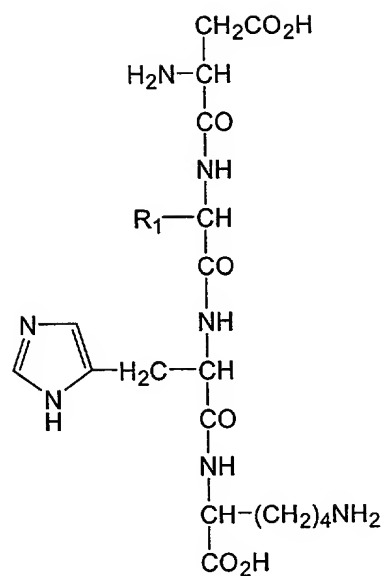
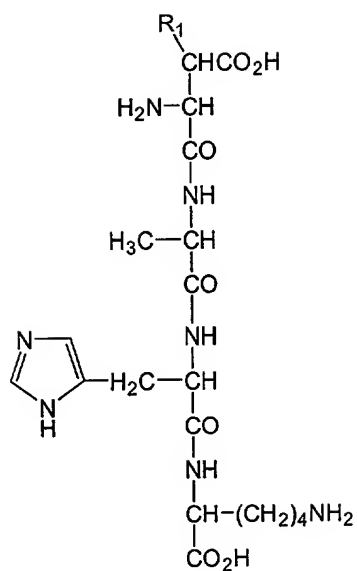
26. The method of Claim 23 wherein at least 50% of the amino acids of P₂ are D-amino acids.

27. The method of Claim 1 wherein at least one amino acid of P₁, at least one amino acid of P₂, or at least one amino acid of P₁ and at least one amino acid of P₂, is substituted

with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

28. The method of Claim 27 wherein n is 0 and P_1 has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R₃ is H, a non-peptide, metal-binding functional group or the two R₃ groups together form a non-peptide, metal-binding functional group.

29. The method of Claim 1 wherein the method further comprises administering an effective amount of another metal-binding compound in combination with the peptide.

30. The method of Claim 29 wherein the metal-binding compound binds iron.

31. The method of Claim 30 wherein the iron-binding compound is deferoxamine mesylate.

32. The method of Claim 29 wherein the metal-binding compound binds Cu(I).

33. The method of Claim 32 wherein the Cu(I)-binding compound is a peptide.

34. The method of Claim 33 wherein the Cu(I)-binding peptide comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,

Cys Cys

Cys Xaa₄ Cys,

Cys Xaa₄ Xaa₄ Cys,

Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,

Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],

Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],

Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or

γ-Glu Cys Gly.

35. The method of Claim 27 wherein the method further comprises administering an effective amount of another metal-binding compound in combination with the peptide.

36. The method of any one of Claims 1-35 wherein the peptide is administered to the animal because of the need to reperfuse an ischemic tissue or organ of the animal.

37. The method of Claim 36 wherein the animal is suffering from cerebrovascular ischemia and the ischemic tissue is located in the brain of the animal.

38. The method of Claim 36 wherein the animal is suffering from cardiovascular

ischemia and the ischemic tissue is located in the heart of the animal.

39. The method of Claim 36 wherein the peptide is administered prior to reperfusion, simultaneously with reperfusion, after reperfusion, or combinations thereof.

40. The method of any one of Claims 1-35 wherein the peptide is administered to the animal because it is suffering from a neurological trauma.

41. The method of any one of Claims 1-35 wherein the peptide is administered to the animal because it is suffering from a neurodegenerative disease.

42. The method of any one of Claims 1-35 wherein the peptide is administered to the animal to reduce the damage done by ROS to its DNA.

43. The method of Claim 42 wherein the DNA comprises telomere DNA.

44. The method of any one of Claims 1-35 wherein the peptide is administered to the animal because it is suffering from inflammation.

45. The method of any one of Claims 1-35 wherein the peptide is administered to the animal because it is suffering from a disease or condition involving acidosis.

46. The method of any one of Claims 1-35 wherein the peptide is administered to the animal because it is suffering from sepsis.

48. The method of any one of Claims 1-35 wherein the peptide is administered prophylactically.

49. The method of Claim 48 wherein the peptide is administered to an animal exhibiting symptoms of possible cerebrovascular ischemia or possible cardiovascular ischemia while the animal is being diagnosed.

50. The method of Claim 48 wherein the peptide is administered to an animal prior to surgery, during surgery, after surgery, or combinations thereof.

51. The method of Claim 50 wherein the surgery is open-heart surgery or surgery to transplant an organ into the animal.

52. The method of Claim 48 wherein the peptide is administered to an animal prior to radiation therapy, during radiation therapy, after radiation therapy, or combinations thereof.

53. A method of reducing the damage done by reactive oxygen species (ROS) to a cell, a tissue or an organ that has been removed from an animal comprising contacting the cell, tissue or organ with a solution or medium containing an effective amount of a peptide having the formula:

$$P_1 - P_2,$$

wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

54. The method of Claim 53 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

55. The method of Claim 53 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

56. The method of Claim 53 wherein Xaa₃ is lysine.

57. The method of Claim 53 wherein Xaa₁ is aspartic acid, glutamic acid, arginine,

threonine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

58. The method of Claim 57 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

59. The method of Claim 58 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

60. The method of Claim 59 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

61. The method of Claim 53 wherein n is 0-10.

62. The method of Claim 61 wherein n is 0-5.

63. The method of Claim 62 wherein n is 0.

64. The method of Claim 53 wherein P₂ comprises a metal-binding sequence.

65. The method of Claim 64 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

66. The method of Claim 65 wherein Xaa₅ is Orn or Lys.

67. The method of Claim 64 wherein P₂ comprises one of the following sequences:

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

[(Xaa₄)_mXaa₅Xaa₂His]_r,

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃(Xaa₄)_mXaa₅Xaa₂His]_r, or

[(Xaa₄)_mXaa₅Xaa₂His(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂, m is 0-5 and r is 2-100.

68. The method of Claim 64 wherein P₂ comprises a sequence which binds Cu(I).

69. The method of Claim 68 wherein P₂ comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,
 Cys Cys,
 Cys Xaa₄ Cys,
 Cys Xaa₄ Xaa₄ Cys,
 Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,
 Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],
 Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],
 Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or
 γ-Glu Cys Gly.

70. The method of Claim 69 wherein P₂ is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

71. The method of Claim 53 wherein P₂ comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

72. The method of Claim 71 wherein P₂ is hydrophobic or an arginine oligomer.

73. The method of Claim 53 wherein at least one of the amino acids of P₁ other than β-alanine, when present, is a D-amino acid.

74. The method of Claim 73 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids.

75. The method of Claim 74 wherein all of the amino acids of P₁ other than β-alanine, when present, are D-amino acids.

76. The method of Claim 73 wherein at least 50% of the amino acids of P₂ are D-amino acids.

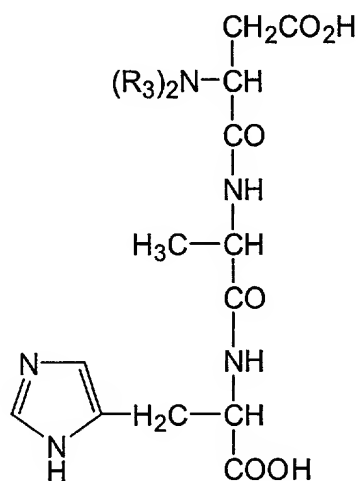
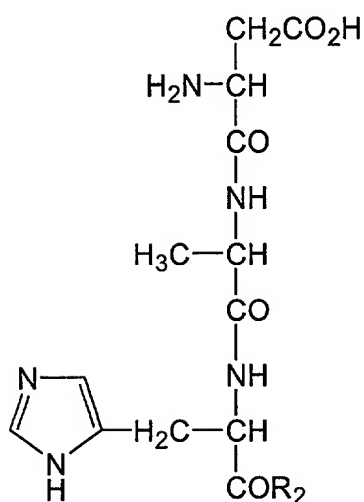
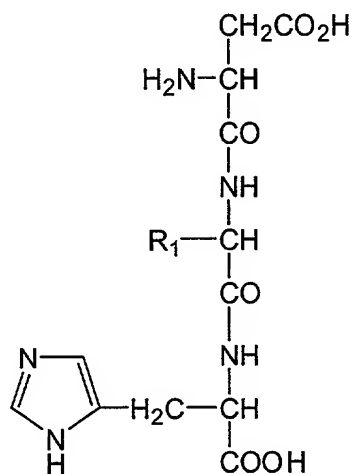
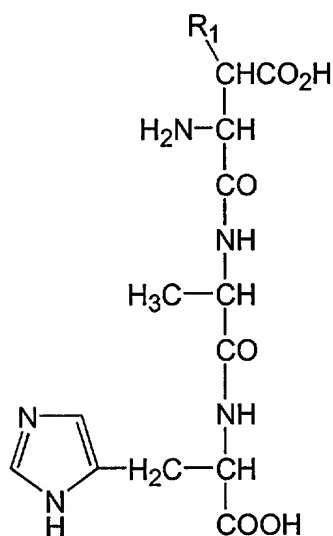
77. The method of Claim 74 wherein at least 50% of the amino acids of P₂ are D-amino acids.

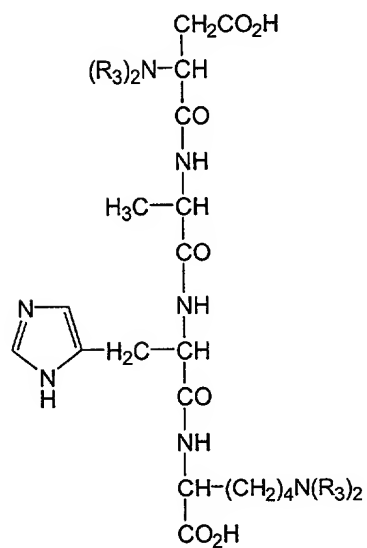
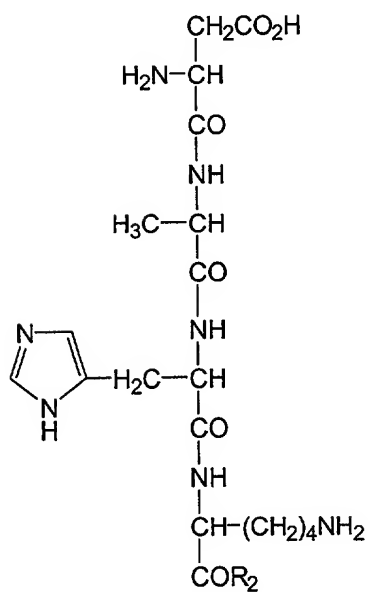
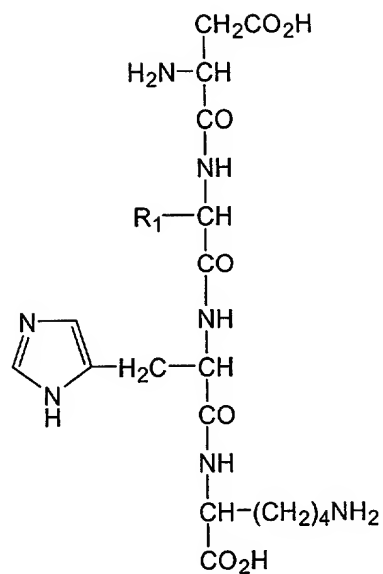
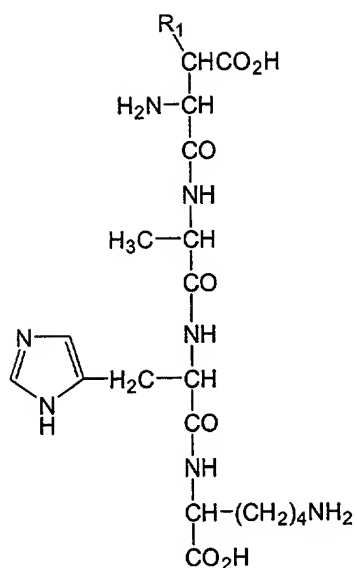
78. The method of Claim 75 wherein at least 50% of the amino acids of P₂ are D-amino acids.

79. The method of Claim 53 wherein at least one amino acid of P₁, at least one amino acid of P₂, or at least one amino acid of P₁ and at least one amino acid of P₂, is substituted

with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

80. The method of Claim 79 wherein n is 0 and P_1 has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

81. The method of Claim 53 wherein the solution of medium further comprises an effective amount of another metal-binding compound in combination with the peptide.

82. The method of any one of Claims 53-81 wherein the cell, tissue or organ is transplanted into an animal after being contacted with the solution or medium containing the peptide.

83. A method of reducing the concentration of a metal in an animal in need thereof comprising administering to the animal an effective amount of a peptide having the formula:

$$P_1 - P_2,$$

wherein:

P_1 is:

$Xaa_1 Xaa_2 His$: or

$Xaa_1 Xaa_2 His Xaa_3$;

P_2 is $(Xaa_4)_n$;

Xaa_1 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_2 is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_3 is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa_4 is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

84. The method of Claim 83 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

85. The method of Claim 83 wherein Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

86. The method of Claim 83 wherein Xaa_3 is lysine.

87. The method of Claim 83 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa_3 is

lysine.

88. The method of Claim 87 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

89. The method of Claim 88 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

90. The method of Claim 89 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

91. The method of Claim 83 wherein n is 0-10.

92. The method of Claim 83 wherein P₂ comprises a metal-binding sequence.

93. The method of Claim 92 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,
 (Xaa₄)_m His Xaa₂ Xaa₅,
 (Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or
 (Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

94. The method of Claim 93 wherein Xaa₅ is Orn or Lys.

95. The method of Claim 92 wherein P₂ comprises one of the following sequences:

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,
 [(Xaa₄)_mXaa₅Xaa₂His]_r,
 [(Xaa₄)_mXaa₅Xaa₂HisXaa₃(Xaa₄)_mXaa₅Xaa₂His]_r, or
 [(Xaa₄)_mXaa₅Xaa₂His(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂, m is 0-5 and r is 2-100.

96. The method of Claim 92 wherein P₂ comprises a sequence which binds Cu(I).

97. The method of Claim 96 wherein P₂ comprises one of the following sequences:

Met Xaa₄ Met,
 Met Xaa₄ Xaa₄ Met,
 Cys Cys,
 Cys Xaa₄ Cys,
 Cys Xaa₄ Xaa₄ Cys,

Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,
 Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],
 Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],
 Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or
 γ-Glu Cys Gly.

98. The method of Claim 97 wherein P₂ is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

99. The method of Claim 83 wherein P₂ comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

100. The method of Claim 99 wherein P₂ is hydrophobic or an arginine oligomer.

101. The method of Claim 83 wherein at least one of the amino acids of P₁ other than β-alanine, when present, is a D-amino acid.

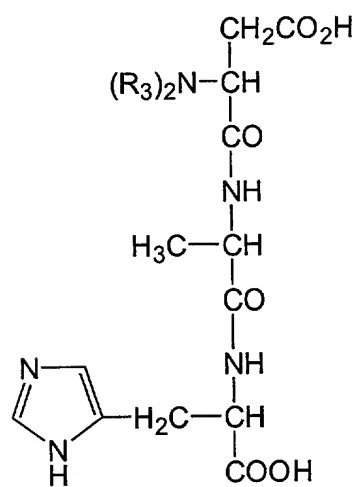
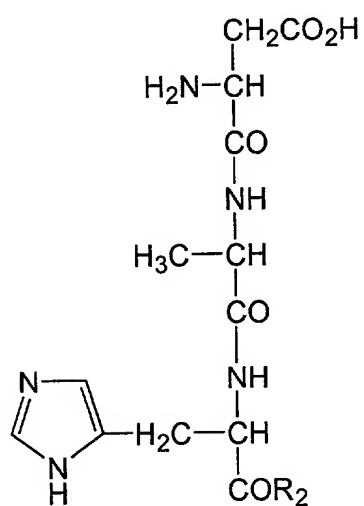
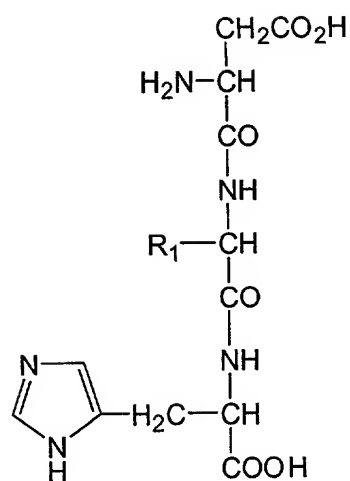
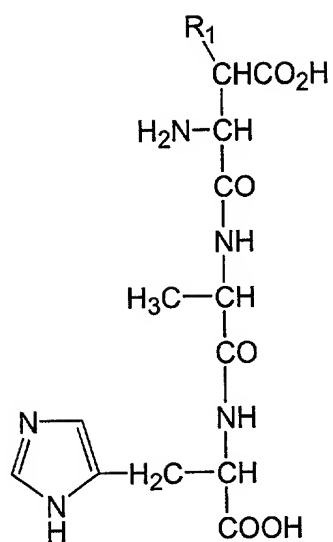
102. The method of Claim 101 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids.

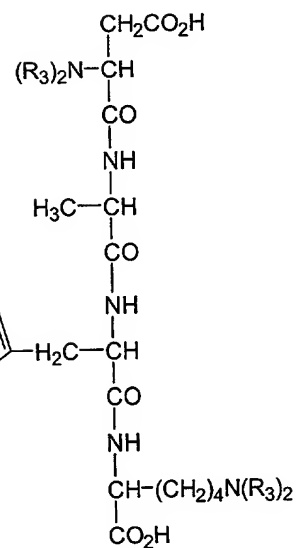
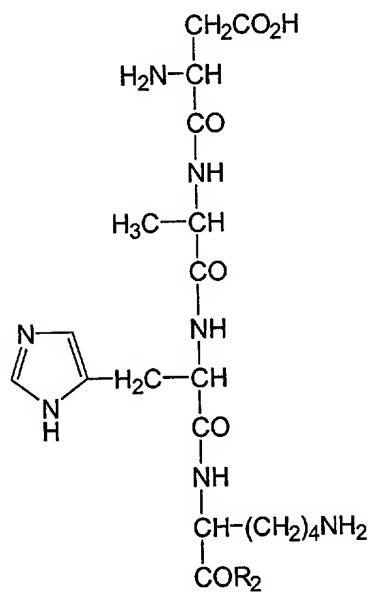
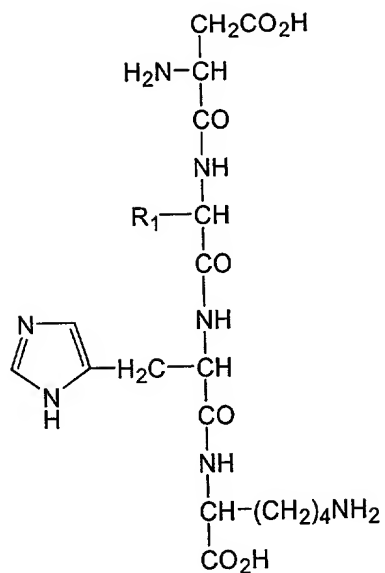
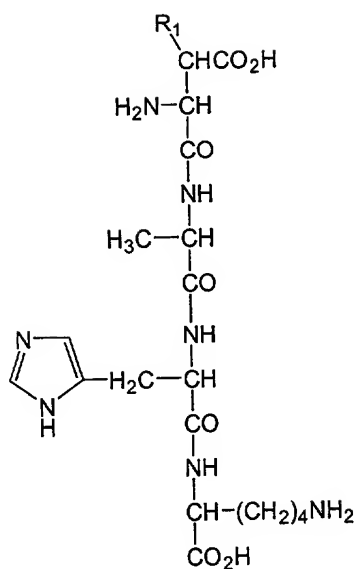
103. The method of Claim 102 wherein all of the amino acids of P₁ other than β-alanine, when present, are D-amino acids.

104. The method of Claim 101 wherein at least 50% of the amino acids of P₂ are D-amino acids.

105. The method of Claim 83 wherein at least one amino acid of P₁, at least one amino acid of P₂, or at least one amino acid of P₁ and at least one amino acid of P₂ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₁ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₁ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

106. The method of Claim 105 wherein n is 0 and P₁ has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

107. The method of Claim 83 wherein the method further comprises administering an effective amount of another metal-binding compound in combination with the peptide.

108. The method of Claim 107 wherein the metal-binding compound binds iron.

109. The method of Claim 108 wherein the iron-binding compound is deferoxamine mesylate.

110. The method of Claim 107 wherein the metal-binding compound binds Cu(I).

111. The method of Claim 110 wherein the Cu(I)-binding compound is a peptide.

112. The method of Claim 111 wherein the Cu(I)-binding peptide comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,

Cys Cys

Cys Xaa₄ Cys,

Cys Xaa₄ Xaa₄ Cys,

Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,

Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],

Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],

Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or

γ -Glu Cys Gly,

wherein Xaa₄ is any amino acid.

113. The method of any one of Claims 83-112 wherein the peptide is administered to the animal to treat an angiogenic disease or condition.

114. The method of Claim 113 wherein the angiogenic disease or condition is a neoplastic disease, a connective tissue disorder, psoriasis, an ocular angiogenic disease, a cardiovascular disease, a cerebral vascular disease, hemophiliac joints, an immune disorder, a benign tumor, hypertrophy, endometriosis, polyposis, or obesity.

115. The method of Claim 114 wherein the neoplastic disease is a tumor.
116. The method of Claim 114 wherein the neoplastic disease is tumor metastasis.
117. The method of any one of Claims 83-112 wherein the peptide is administered to the animal to inhibit the vascularization required for embryo implantation.
118. The method of any one of Claims 83-112 wherein the peptide is administered to the animal to treat a cancer or to inhibit carcinogenesis.

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119. A method of reducing the damage done by reactive oxygen species (ROS) in an animal comprising administering to the animal an effective amount of a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

120. The method of Claim 119 wherein the peptide contains from 2-10 amino acids.

121. The method of Claim 120 wherein the peptide contains from 3-5 amino acids.

122. The method of Claim 119 wherein the amino acids of the peptide are D-amino acids.

123. The method of Claim 119 wherein the method further comprises administering an effective amount of a second metal-binding compound.

119. A method of reducing the damage done by reactive oxygen species (ROS) in an animal comprising administering to the animal an effective amount of a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

124. A method of reducing the damage done by reactive oxygen species (ROS) to a cell, a tissue or an organ that has been removed from an animal comprising contacting the cell, tissue or organ with a solution or medium containing an effective amount of a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

125. The method of Claim 124 wherein the peptide contains from 2-10 amino acids.

126. The method of Claim 125 wherein the peptide contains from 3-5 amino acids.

127. The method of Claim 124 wherein the amino acids of the peptide are D-amino acids.

128. The method of Claim 124 wherein the solution or medium further comprises an effective amount of a second metal-binding compound.

129. A method of reducing the concentration of metal in an animal in need thereof comprising administering to the animal an effective amount of a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

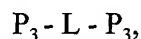
130. The method of Claim 129 wherein the peptide contains from 2-10 amino acids.

131. The method of Claim 130 wherein the peptide contains from 3-5 amino acids.

132. The method of Claim 129 wherein the amino acids of the peptide are D-amino acids.

133. The method of Claim 129 wherein the method further comprises administering an effective amount of a second metal-binding compound.

134. A method of reducing the damage done by reactive oxygen species (ROS) in an animal comprising administering to the animal an effective amount of a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

135. The method of Claim 134 wherein each P_3 contains 2-10 amino acids.

136. The method of Claim 134 wherein at least one P_3 is P_1 , wherein P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃; and

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

137. The method of Claim 136 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

138. The method of Claim 136 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

139. The method of Claim 136 wherein Xaa₃ is lysine.

140. The method of Claim 136 wherein Xaa₁ is aspartic acid, glutamic acid, arginine,

threonine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

141. The method of Claim 140 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

142. The method of Claim 141 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

143. The method of Claim 142 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

144. The method of Claim 136 wherein at least one amino acid of P₁ other than β -alanine, when present, is a D-amino acid.

145. The method of Claim 144 wherein all of the amino acids of P₁ other than β -alanine, when present, are D-amino acids.

146. The method of Claim 136 wherein both P₃ peptides are P₁.

147. The method of Claim 134 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₃ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

148. The method of Claim 134 wherein P₃ comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P₃.

149. The method of Claim 134 wherein L is neutral.

150. The method of Claim 134 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

151. The method of Claim 150 wherein L contains 2-8 carbon atoms.

152. The method of Claim 134 wherein L is a cyclic alkane residue containing from 2-8 carbon atoms.

153. The method of Claim 152 wherein L contains 3-5 carbon atoms.

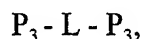
154. The method of Claim 134 wherein L is a nitrogen-containing heterocyclic alkane residue.

155. The method of Claim 154 wherein L is a piperazide.

156. The method of Claim 134 wherein L is a glyceryl ester.

157. The method of Claim 134 wherein the method further comprises administering an effective amount of another metal-binding compound in combination with the peptide dimer.

158. A method of reducing the damage done by reactive oxygen species (ROS) to a cell, a tissue or an organ that has been removed from an animal comprising contacting the cell, tissue or organ with a solution or medium containing an effective amount of a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

159. The method of Claim 158 wherein each P_3 contains 2-10 amino acids.

160. The method of Claim 158 wherein at least one P_3 is P_1 , wherein P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃; and

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

161. The method of Claim 160 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

162. The method of Claim 160 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

163. The method of Claim 160 wherein Xaa₃ is lysine.

164. The method of Claim 160 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

165. The method of Claim 164 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

166. The method of Claim 165 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

167. The method of Claim 166 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

168. The method of Claim 160 wherein at least one amino acid of P₁ other than β -alanine, when present, is a D-amino acid.

169. The method of Claim 168 wherein all of the amino acids of P₁ other than β -alanine, when present, are D-amino acids.

170. The method of Claim 160 wherein both P₃ peptides are P₁.

171. The method of Claim 158 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₃ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

172. The method of Claim 158 wherein P₃ comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P₃.

173. The method of Claim 158 wherein L is neutral.

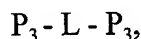
174. The method of Claim 158 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

175. The method of Claim 174 wherein L contains 2-8 carbon atoms.

176. The method of Claim 158 wherein L is a cyclic alkane residue containing from 2-8 carbon atoms.

177. The method of Claim 176 wherein L contains 3-5 carbon atoms.
178. The method of Claim 158 wherein L is a nitrogen-containing heterocyclic alkane residue.
179. The method of Claim 178 wherein L is a piperazide.
180. The method of Claim 158 wherein L is a glyceryl ester.
181. The method of Claim 158 wherein the solution or medium further comprises an effective amount of another metal-binding compound in combination with the peptide dimer.

182. A method of reducing the concentration of a metal in an animal in need thereof comprising administering to the animal an effective amount of a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

183. The method of Claim 182 wherein each P_3 contains 2-10 amino acids.

184. The method of Claim 182 wherein at least one P_3 is P_1 , wherein P_1 is:

$Xaa_1 Xaa_2 His$; or

$Xaa_1 Xaa_2 His Xaa_3$; and

Xaa_1 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_2 is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa_3 is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

185. The method of Claim 184 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

186. The method of Claim 184 wherein Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

187. The method of Claim 184 wherein Xaa_3 is lysine.

188. The method of Claim 184 wherein Xaa_1 is aspartic acid, glutamic acid, arginine,

threonine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

189. The method of Claim 188 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

190. The method of Claim 189 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

191. The method of Claim 190 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

192. The method of Claim 184 wherein at least one amino acid of P₁ other than β -alanine, when present, is a D-amino acid.

193. The method of Claim 192 wherein all of the amino acids of P₁ other than β -alanine, when present, are D-amino acids.

194. The method of Claim 184 wherein both P₃ peptides are P₁.

195. The method of Claim 182 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₃ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

196. The method of Claim 182 wherein P₃ comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P₃.

197. The method of Claim 182 wherein L is neutral.

198. The method of Claim 182 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

199. The method of Claim 198 wherein L contains 2-8 carbon atoms.

200. The method of Claim 182 wherein L is a cyclic alkane residue containing from 2-8 carbon atoms.

201. The method of Claim 200 wherein L contains 3-5 carbon atoms.

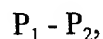
202. The method of Claim 182 wherein L is a nitrogen-containing heterocyclic alkane residue.

203. The method of Claim 202 wherein L is a piperazide.

204. The method of Claim 182 wherein L is a glyceryl ester.

205. The method of Claim 182 wherein the method further comprises administering an effective amount of another metal-binding compound in combination with the peptide dimer.

206. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

207. The composition of Claim 206 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

208. The composition of Claim 206 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

209. The composition of Claim 206 wherein Xaa₃ is lysine.

210. The composition of Claim 206 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and

Xaa₃ is lysine.

211. The composition of Claim 210 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

212. The composition of Claim 211 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

213. The composition of Claim 212 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

214. The composition of Claim 206 wherein n is 0-10.

215. The composition of Claim 214 wherein n is 0-5.

216. The composition of Claim 215 wherein n is 0.

217. The composition of Claim 206 wherein P₂ comprises a metal-binding sequence.

218. The composition of Claim 217 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

219. The composition of Claim 218 wherein Xaa₅ is Orn or Lys.

220. The composition of Claim 217 wherein P₂ comprises one of the following sequences:

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

[(Xaa₄)_mXaa₅Xaa₂His]_r,

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃(Xaa₄)_mXaa₅Xaa₂His]_r, or

[(Xaa₄)_mXaa₅Xaa₂His(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂, m is 0-5 and r is 2-100.

221. The composition of Claim 217 wherein P₂ comprises a sequence which binds Cu(I).

222. The composition of Claim 221 wherein P₂ comprises one of the following

sequences:

Met Xaa₄ Met,
 Met Xaa₄ Xaa₄ Met,
 Cys Cys,
 Cys Xaa₄ Cys,
 Cys Xaa₄ Xaa₄ Cys,
 Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,
 Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],
 Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],
 Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or
 γ-Glu Cys Gly.

223. The composition of Claim 222 wherein P₂ is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

224. The composition of Claim 206 wherein P₂ comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

225. The composition of Claim 224 wherein P₂ is hydrophobic or an arginine oligomer.

226. The composition of Claim 206 wherein at least one of the amino acids of P₁ other than β-alanine, when present, is a D-amino acid.

227. The composition of Claim 226 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids.

228. The composition of Claim 227 wherein all of the amino acids of P₁ other than β-alanine, when present, are D-amino acids.

229. The composition of Claim 226 wherein at least 50% of the amino acids of P₂ are D-amino acids.

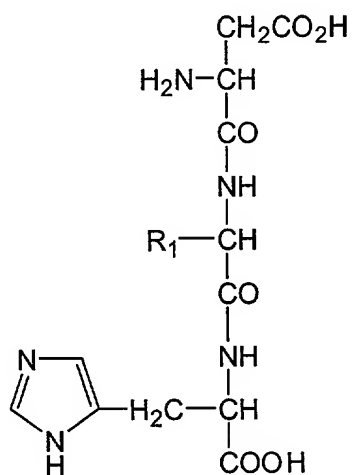
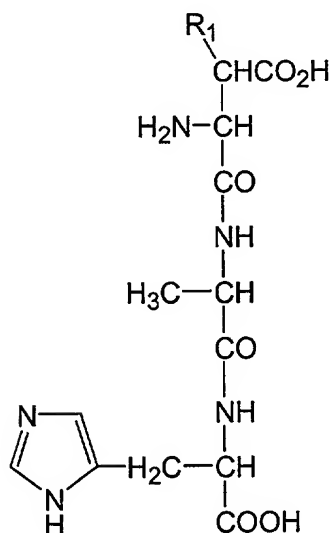
230. The composition of Claim 227 wherein at least 50% of the amino acids of P₂ are D-amino acids.

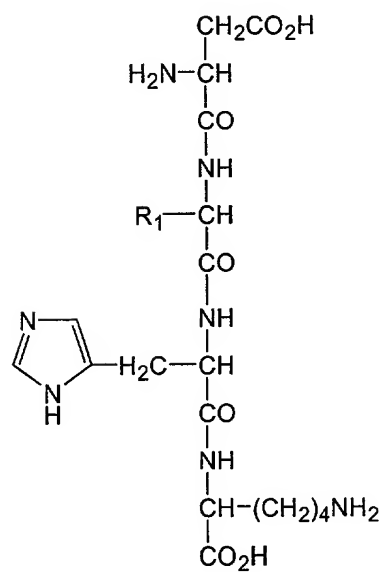
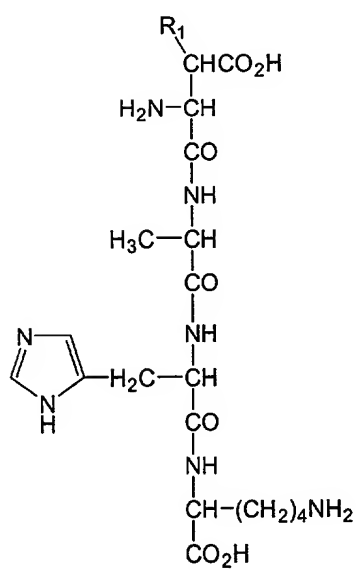
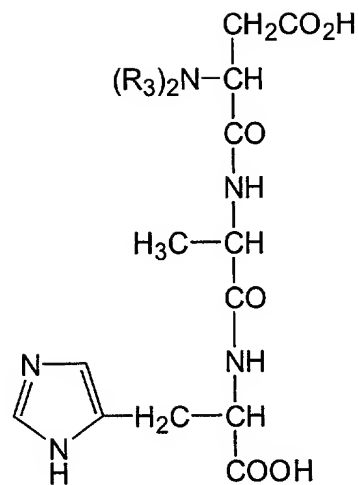
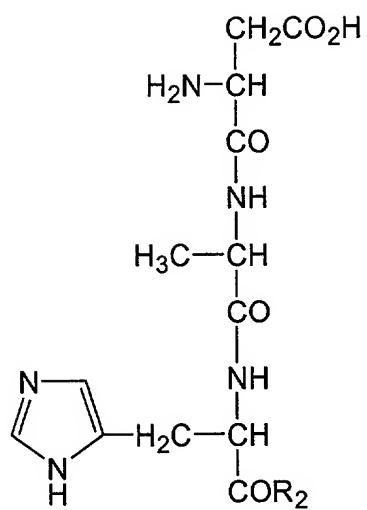
231. The composition of Claim 228 wherein at least 50% of the amino acids of P₂ are

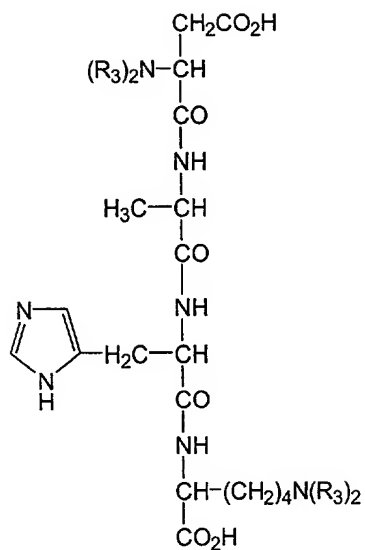
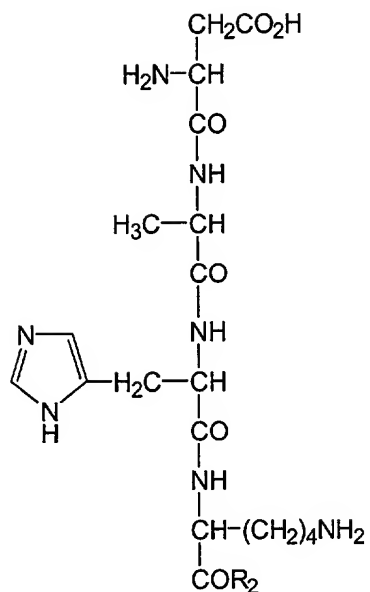
D-amino acids.

232. The composition of Claim 206 wherein at least one amino acid of P_1 , at least one amino acid of P_2 , or at least one amino acid of P_1 and at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

233. The composition of Claim 232 wherein n is 0 and P_1 has one of the following formulas:







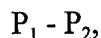
wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-\text{NH}_2$, $-\text{NHR}_1$, $\text{N}(\text{R}_1)_2$, $-\text{OR}_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

234. A kit comprising a container holding a peptide having the formula:



wherein:

P_1 is:

$Xaa_1 Xaa_2 His$: or

$Xaa_1 Xaa_2 His Xaa_3$;

P_2 is $(Xaa_4)_n$;

Xaa_1 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_2 is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_3 is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa_4 is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

235. The kit of Claim 234 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

236. The kit of Claim 234 wherein Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

237. The kit of Claim 234 wherein Xaa_3 is lysine.

238. The kit of Claim 234 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa_3 is lysine.

239. The kit of Claim 238 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α-hydroxymethylserine.

240. The kit of Claim 239 wherein Xaa₂ is alanine, threonine, leucine, or α-hydroxymethylserine.

241. The kit of Claim 240 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

242. The kit of Claim 234 wherein n is 0-10.

243. The kit of Claim 242 wherein n is 0-5.

244. The kit of Claim 243 wherein n is 0.

245. The kit of Claim 234 wherein P₂ comprises a metal-binding sequence.

246. The kit of Claim 245 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

247. The kit of Claim 246 wherein Xaa₅ is Orn or Lys.

248. The kit of Claim 245 wherein P₂ comprises one of the following sequences:

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

[(Xaa₄)_mXaa₅Xaa₂His]_r,

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃(Xaa₄)_mXaa₅Xaa₂His]_r, or

[(Xaa₄)_mXaa₅Xaa₂His(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂, m is 0-5 and r is 2-100.

249. The kit of Claim 245 wherein P₂ comprises a sequence which binds Cu(I).

250. The kit of Claim 249 wherein P₂ comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,

Cys Cys,

Cys Xaa₄ Cys,

Cys Xaa₄ Xaa₄ Cys,
 Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,
 Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],
 Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],
 Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or
 γ-Glu Cys Gly.

251. The kit of Claim 250 wherein P₂ is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

252. The kit of Claim 234 wherein P₂ comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

253. The kit of Claim 252 wherein P₂ is hydrophobic or an arginine oligomer.

254. The kit of Claim 234 wherein at least one of the amino acids of P₁ other than β-alanine, when present, is a D-amino acid.

255. The kit of Claim 254 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids.

256. The kit of Claim 255 wherein all of the amino acids of P₁ other than β-alanine, when present, are D-amino acids.

257. The kit of Claim 254 wherein at least 50% of the amino acids of P₂ are D-amino acids.

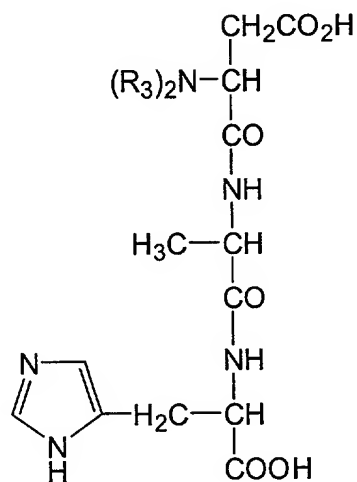
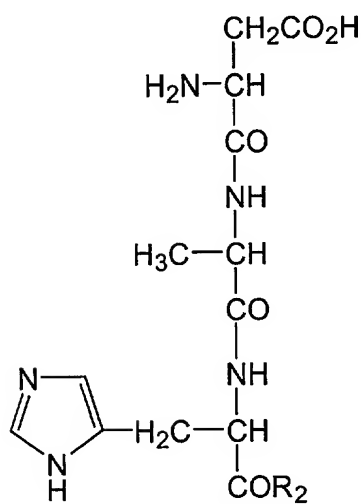
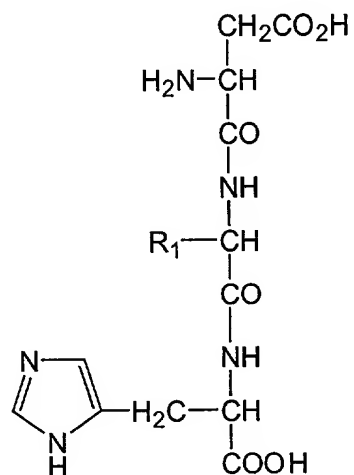
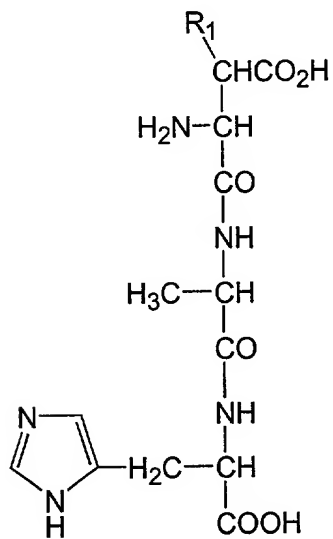
258. The kit of Claim 255 wherein at least 50% of the amino acids of P₂ are D-amino acids.

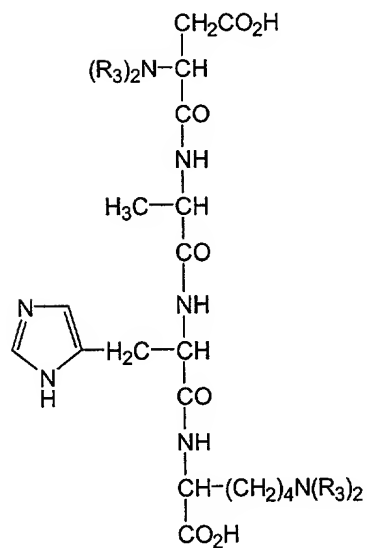
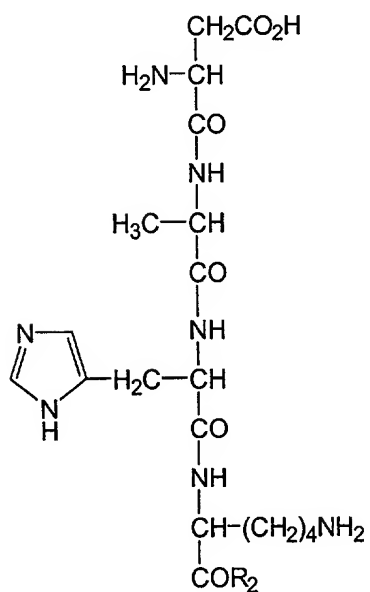
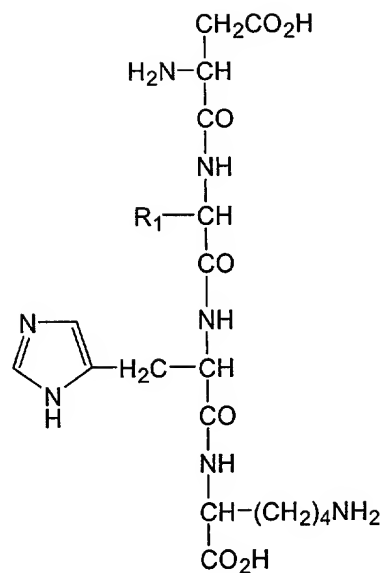
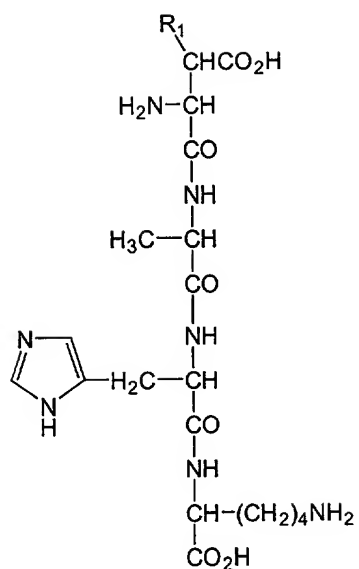
259. The kit of Claim 256 wherein at least 50% of the amino acids of P₂ are D-amino acids.

260. The kit of Claim 234 wherein at least one amino acid of P₁, at least one amino acid of P₂, or at least one amino acid of P₁ and at least one amino acid of P₂ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₁ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₁ to bind metal ions, or (c) a substituent which is a non-peptide,

metal-binding functional group that increases the ability of the peptide to bind metal ions.

261. The kit of Claim 260 wherein n is 0 and P_1 has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

262. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

263. The composition of Claim 262 wherein the peptide contains from 2-10 amino acids.

264. The composition of Claim 263 wherein the peptide contains from 3-5 amino acids.

265. The composition of Claim 262 wherein the amino acids of the peptide are D-amino acids.

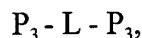
266. A kit comprising a container holding a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

267. The kit of Claim 266 wherein the peptide contains from 2-10 amino acids.

268. The kit of Claim 267 wherein the peptide contains from 3-5 amino acids.

269. The kit of Claim 266 wherein the amino acids of the peptide are D-amino acids.

270. A composition comprising a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

271. The composition of Claim 270 wherein each P_3 contains 2-10 amino acids.

272. The composition of Claim 270 wherein at least one P_3 is P_1 , wherein P_1 is:

$Xaa_1 Xaa_2 His$; or

$Xaa_1 Xaa_2 His Xaa_3$; and

Xaa_1 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_2 is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa_3 is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

273. The composition of Claim 272 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

274. The composition of Claim 272 wherein Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

275. The composition of Claim 272 wherein Xaa_3 is lysine.

276. The composition of Claim 272 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and

Xaa₃ is lysine.

277. The composition of Claim 276 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

278. The composition of Claim 277 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

279. The composition of Claim 278 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

280. The composition of Claim 272 wherein at least one amino acid of P₁ other than β -alanine, when present, is a D-amino acid.

281. The composition of Claim 280 wherein all of the amino acids of P₁ other than β -alanine, when present, are D-amino acids.

282. The composition of Claim 272 wherein both P₃ peptides are P₁.

283. The composition of Claim 270 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₃ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

284. The composition of Claim 270 wherein P₃ comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P₃.

285. The composition of Claim 270 wherein L is neutral.

286. The composition of Claim 270 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

287. The composition of Claim 286 wherein L contains 2-8 carbon atoms.

288. The composition of Claim 270 wherein L is a cyclic alkane residue containing from 2-8 carbon atoms.

289. The composition of Claim 288 wherein L contains 3-5 carbon atoms.

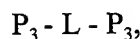
290. The composition of Claim 270 wherein L is a nitrogen-containing heterocyclic

alkane residue.

291. The composition of Claim 290 wherein L is a piperazide.

292. The composition of Claim 270 wherein L is a glyceryl ester.

293. A kit comprising a container holding a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

294. The kit of Claim 293 wherein each P_3 contains 2-10 amino acids.

295. The kit of Claim 293 wherein at least one P_3 is P_1 , wherein P_1 is:

$Xaa_1 Xaa_2 His$: or

$Xaa_1 Xaa_2 His Xaa_3$; and

Xaa_1 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_2 is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa_3 is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

296. The kit of Claim 295 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

297. The kit of Claim 295 wherein Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

298. The kit of Claim 295 wherein Xaa_3 is lysine.

299. The kit of Claim 295 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa_2 is glycine, alanine, valine, leucine, isoleucine,

threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

300. The kit of Claim 299 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

301. The kit of Claim 300 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

302. The kit of Claim 301 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

303. The kit of Claim 295 wherein at least one amino acid of P₁ other than β -alanine, when present, is a D-amino acid.

304. The kit of Claim 303 wherein all of the amino acids of P₁ other than β -alanine, when present, are D-amino acids.

305. The kit of Claim 295 wherein both P₃ peptides are P₁.

306. The kit of Claim 293 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₃ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

307. The kit of Claim 293 wherein P₃ comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P₃.

308. The kit of Claim 293 wherein L is neutral.

309. The kit of Claim 293 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

310. The kit of Claim 309 wherein L contains 2-8 carbon atoms.

311. The kit of Claim 293 wherein L is a cyclic alkane residue containing from 2-8 carbon atoms.

312. The kit of Claim 311 wherein L contains 3-5 carbon atoms.

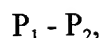
313. The kit of Claim 293 wherein L is a nitrogen-containing heterocyclic alkane

residue.

314. The kit of Claim 313 wherein L is a piperazide.

315. The kit of Claim 293 wherein L is a glyceryl ester.

316. A peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid;

n is 0-100; and

at least one amino acid of P_1 is a D-amino acid;

or a physiologically-acceptable salt thereof.

317. The peptide of Claim 316 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

318. The peptide of Claim 316 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

319. The peptide of Claim 316 wherein Xaa₃ is lysine.

320. The peptide of Claim 316 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is

lysine.

321. The peptide of Claim 320 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α-hydroxymethylserine.

322. The peptide of Claim 321 wherein Xaa₂ is alanine, threonine, leucine, or α-hydroxymethylserine.

323. The peptide of Claim 322 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

324. The peptide of Claim 316 wherein n is 0-10.

325. The peptide of Claim 324 wherein n is 0-5.

326. The peptide of Claim 325 wherein n is 0.

327. The peptide of Claim 316 wherein P₂ comprises a metal-binding sequence.

328. The peptide of Claim 327 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

329. The peptide of Claim 328 wherein Xaa₅ is Orn or Lys.

330. The peptide of Claim 327 wherein P₂ comprises one of the following sequences:

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

[(Xaa₄)_mXaa₅Xaa₂His]_r,

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃(Xaa₄)_mXaa₅Xaa₂His]_r, or

[(Xaa₄)_mXaa₅Xaa₂His(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂, m is 0-5 and r is 2-100.

331. The peptide of Claim 327 wherein P₂ comprises a sequence which binds Cu(I).

332. The peptide of Claim 331 wherein P₂ comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,

Cys Cys,

Cys Xaa₄ Cys,
 Cys Xaa₄ Xaa₄ Cys,
 Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,
 Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],
 Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],
 Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or
 γ-Glu Cys Gly.

333. The peptide of Claim 332 wherein P₂ is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

334. The peptide of Claim 316 wherein P₂ comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

335. The peptide of Claim 334 wherein P₂ is hydrophobic or an arginine oligomer.

336. The peptide of Claim 316 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids.

337. The peptide of Claim 336 wherein all of the amino acids of P₁ other than β-alanine, when present, are D-amino acids.

338. The peptide of Claim 316 wherein at least 50% of the amino acids of P₂ are D-amino acids.

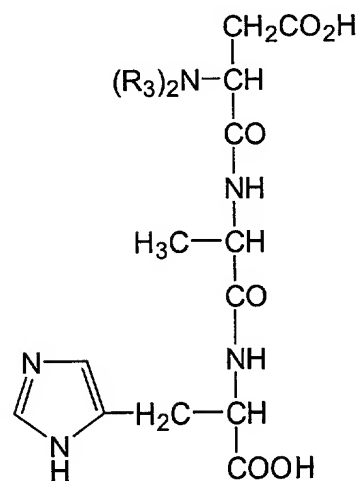
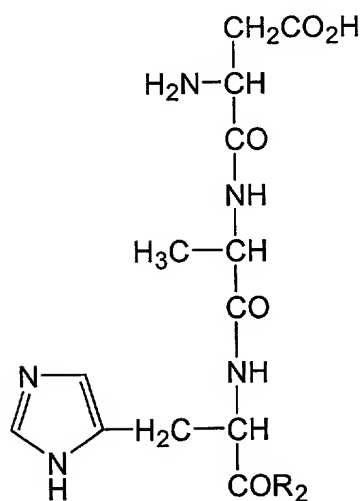
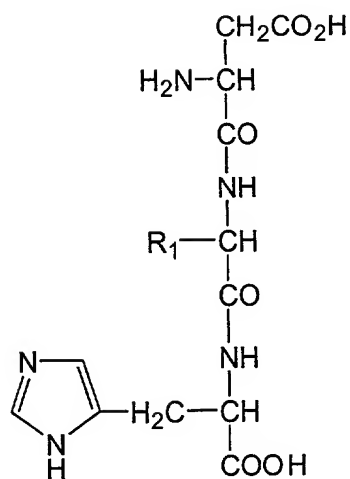
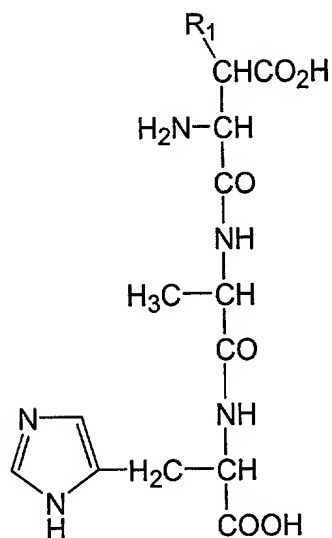
339. The peptide of Claim 336 wherein at least 50% of the amino acids of P₂ are D-amino acids.

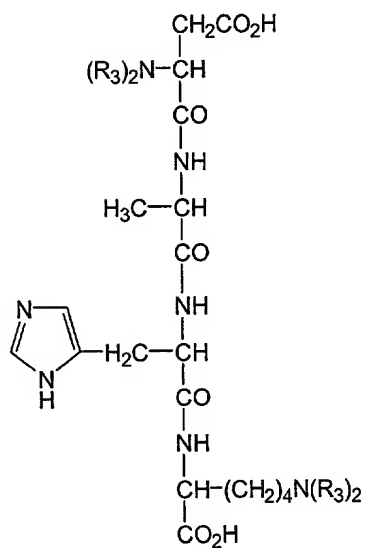
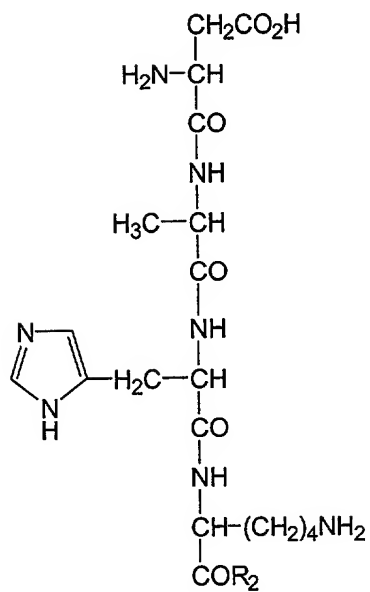
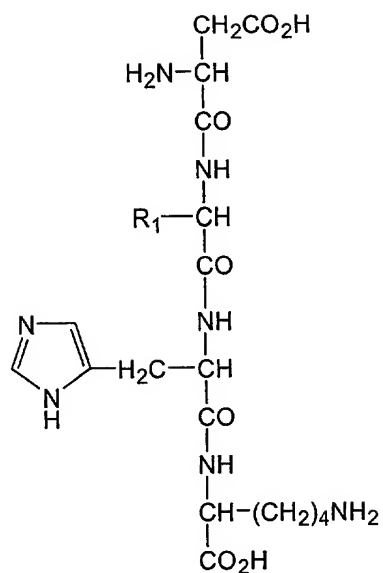
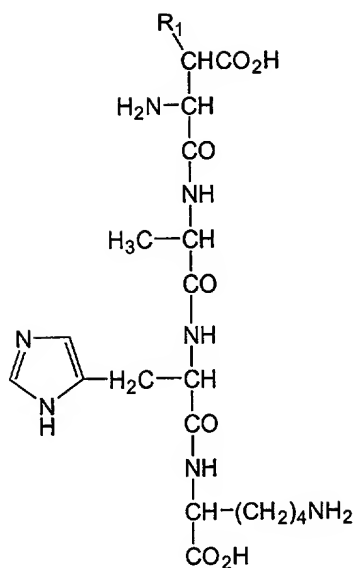
340. The peptide of Claim 337 wherein at least 50% of the amino acids of P₂ are D-amino acids.

341. The peptide of Claim 316 wherein at least one amino acid of P₁, at least one amino acid of P₂, or at least one amino acid of P₁ and at least one amino acid of P₂ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₁ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₁ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide

to bind metal ions.

342. The peptide of Claim 341 n is 0 and wherein P_1 has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

343. A peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid;

n is 0-100; and

at least one amino acid of P_1 , at least one amino acid of P_2 , or at least one amino acid of P_1 and at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.;

or a physiologically-acceptable salt thereof.

344. The peptide of Claim 343 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

345. The peptide of Claim 343 wherein Xaa₂ is glycine, alanine, valine, leucine,

isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

346. The peptide of Claim 343 wherein Xaa₃ is lysine.

347. The peptide of Claim 343 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

348. The peptide of Claim 347 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

349. The peptide of Claim 348 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

350. The peptide of Claim 349 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

351. The peptide of Claim 343 wherein n is 0-10.

352. The peptide of Claim 351 wherein n is 0-5.

353. The peptide of Claim 352 wherein n is 0.

354. The peptide of Claim 343 wherein P₂ comprises a metal-binding sequence.

355. The peptide of Claim 354 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

356. The peptide of Claim 355 wherein Xaa₅ is Orn or Lys.

357. The peptide of Claim 354 wherein P₂ comprises one of the following sequences:

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

[(Xaa₄)_mXaa₅Xaa₂His]_r,

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃(Xaa₄)_mXaa₅Xaa₂His]_r, or

[(Xaa₄)_mXaa₅Xaa₂His(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂, m is 0-5 and r is 2-100.

358. The peptide of Claim 354 wherein P_2 comprises a sequence which binds Cu(I).

359. The peptide of Claim 358 wherein P_2 comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,

Cys Cys,

Cys Xaa₄ Cys,

Cys Xaa₄ Xaa₄ Cys,

Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,

Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],

Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],

Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or

γ -Glu Cys Gly.

360. The peptide of Claim 359 wherein P_2 is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

361. The peptide of Claim 343 wherein P_2 comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

362. The peptide of Claim 361 wherein P_2 is hydrophobic or an arginine oligomer.

363. The peptide of Claim 343 wherein at least one of the amino acids of P_1 other than β -alanine, when present, is a D-amino acid.

364. The peptide of Claim 363 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids.

365. The peptide of Claim 364 wherein all of the amino acids of P_1 other than β -alanine, when present, are D-amino acids.

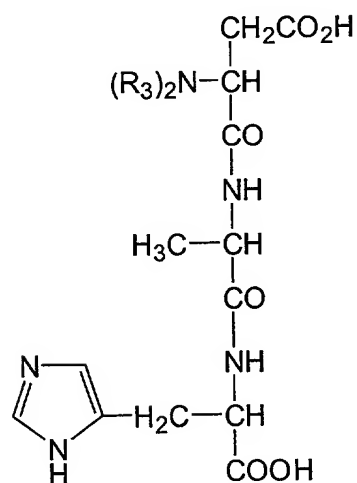
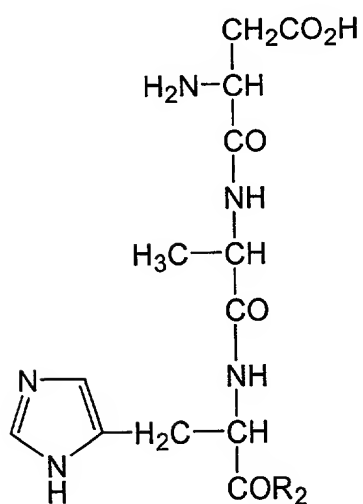
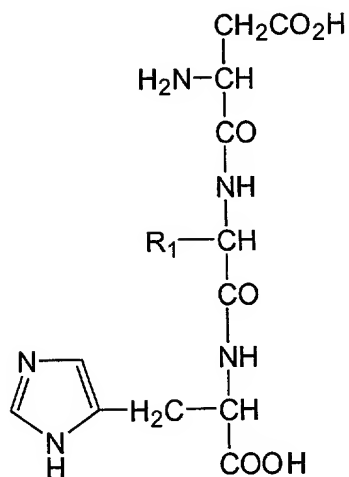
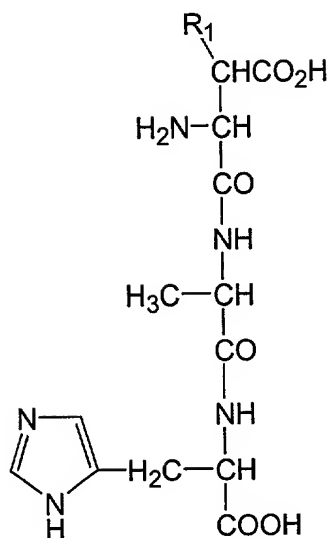
366. The peptide of Claim 363 wherein at least 50% of the amino acids of P_2 are D-amino acids.

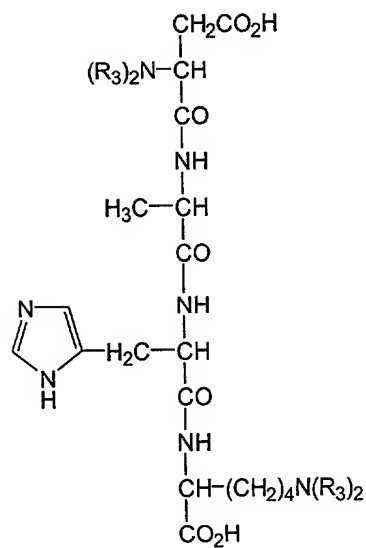
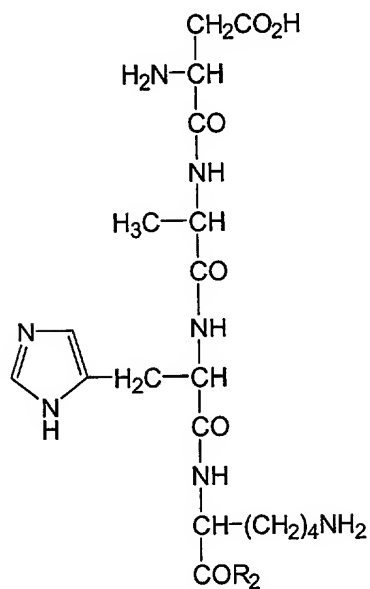
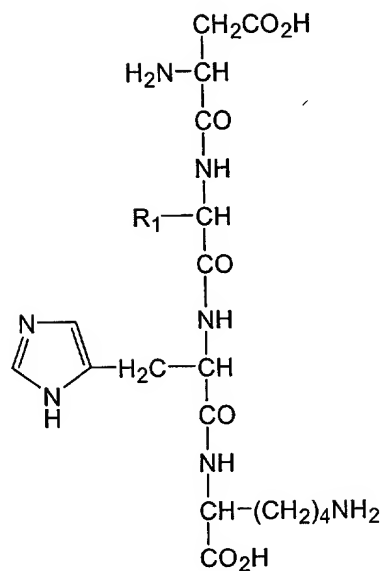
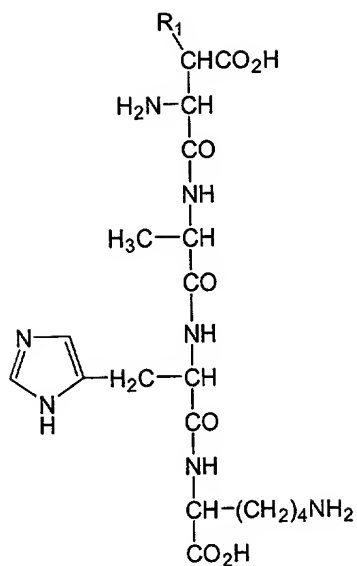
367. The peptide of Claim 364 wherein at least 50% of the amino acids of P_2 are D-amino acids.

368. The peptide of Claim 365 wherein at least 50% of the amino acids of P_2 are D-

amino acids.

369. The peptide of Claim 343 wherein n is 0 and P_1 has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

370. A metal-binding peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is a peptide sequence which comprises the sequence of a metal binding site;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

or a physiologically-acceptable salt thereof.

371. The peptide of Claim 370 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

372. The peptide of Claim 370 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

373. The peptide of Claim 370 wherein Xaa₃ is lysine.

374. The peptide of Claim 370 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

375. The peptide of Claim 374 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

376. The peptide of Claim 375 wherein Xaa₂ is alanine, threonine, leucine, or α-hydroxymethylserine.

377. The peptide of Claim 376 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

378. The peptide of Claim 370 wherein P₂ has one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

Xaa₄ is any amino acid;

Xaa₅ is an amino acid having a free side-chain -NH₂; and

m is 0-5.

379. The peptide of Claim 378 wherein Xaa₅ is Orn or Lys.

380. The peptide of Claim 370 wherein P₂ comprises one of the following sequences:

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

[(Xaa₄)_mXaa₅Xaa₂His]_r,

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃(Xaa₄)_mXaa₅Xaa₂His]_r, or

[(Xaa₄)_mXaa₅Xaa₂His(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

wherein Xaa₄ is any amino acid, Xaa₅ is an amino acid having a free side-chain -NH₂, m is 0-5 and r is 2-100.

381. The peptide of Claim 370 wherein P₂ comprises a sequence which binds Cu(I).

382. The peptide of Claim 381 wherein P₂ comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,

Cys Cys,

Cys Xaa₄ Cys,

Cys Xaa₄ Xaa₄ Cys,

Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,

Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],

Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],
 Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or
 γ -Glu Cys Gly.

383. The peptide of Claim 382 wherein P₂ is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

384. The peptide of Claim 370 wherein at least one amino acid of P₁ other than β -alanine, when present, is a D-amino acid.

385. The peptide of Claim 384 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids.

386. The peptide of Claim 385 wherein all of the amino acids of P₁ other than β -alanine, when present, are D-amino acids.

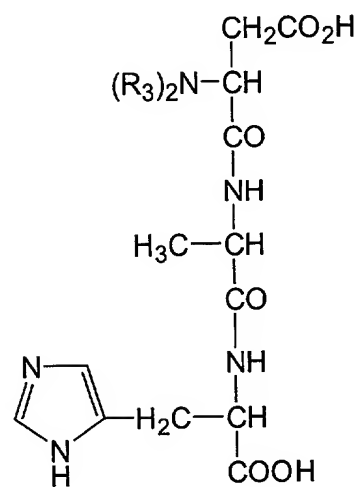
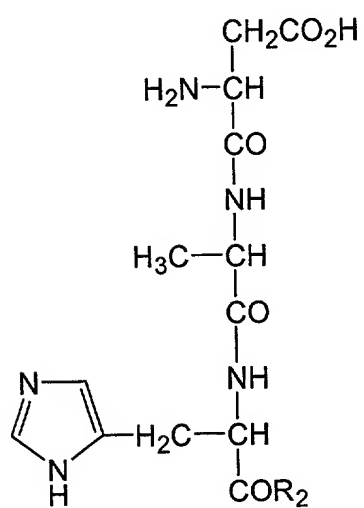
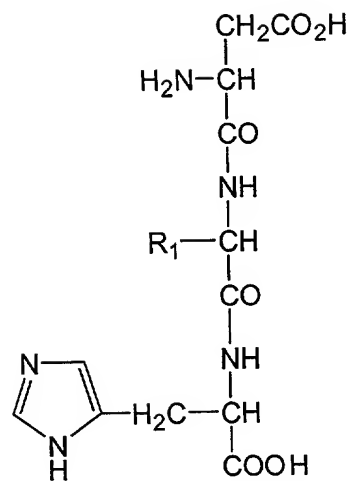
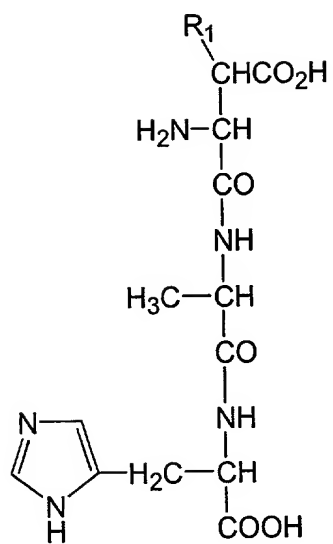
387. The peptide of Claim 384 wherein at least 50% of the amino acids of P₂ are D-amino acids.

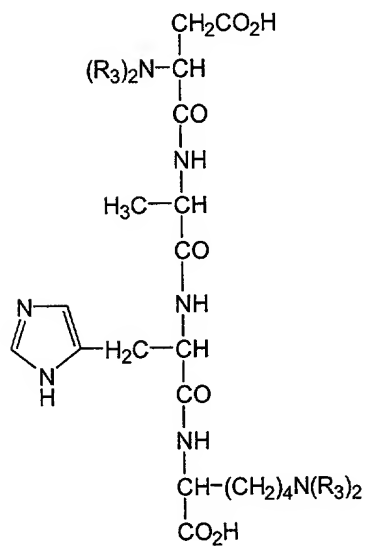
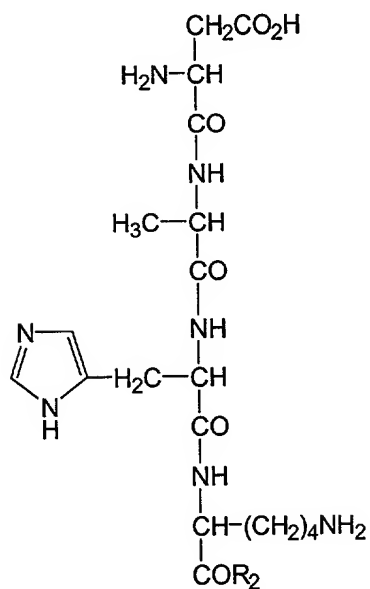
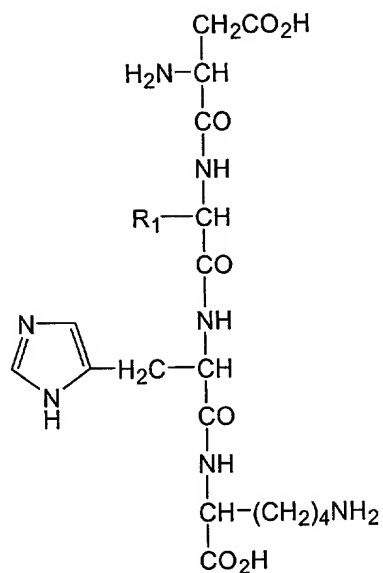
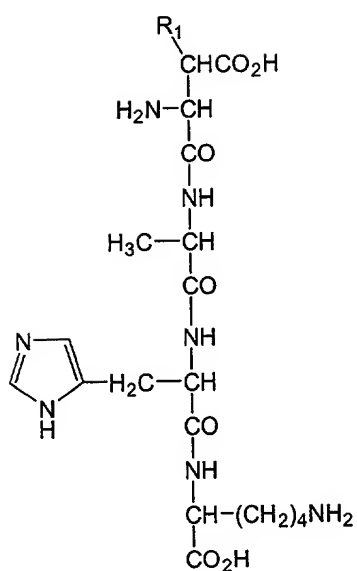
388. The peptide of Claim 385 wherein at least 50% of the amino acids of P₂ are D-amino acids.

389. The peptide of Claim 386 wherein at least 50% of the amino acids of P₂ are D-amino acids.

390. The peptide of Claim 370 wherein at least one amino acid of P₁, at least one amino acid of P₂, or at least one amino acid of P₁ and at least one amino acid of P₂ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₁ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₁ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

391. The peptide of Claim 390 wherein n is 0 and P₁ has one of the following formulas:





wherein:

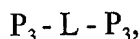
R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

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392. A metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

393. The peptide dimer of Claim 392 wherein each P_3 contains 2-10 amino acids.

394. The peptide dimer of Claim 392 wherein at least one P_3 is P_1 , wherein P_1 is:

$Xaa_1 Xaa_2 His$; or

$Xaa_1 Xaa_2 His Xaa_3$; and

Xaa_1 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_2 is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa_3 is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

395. The peptide dimer of Claim 394 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine.

396. The peptide dimer of Claim 394 wherein Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

397. The peptide dimer of Claim 394 wherein Xaa_3 is lysine.

398. The peptide dimer of Claim 394 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, threonine, or α -hydroxymethylserine, Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and

Xaa₃ is lysine.

399. The peptide dimer of Claim 398 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, leucine, or α -hydroxymethylserine.

400. The peptide dimer of Claim 399 wherein Xaa₂ is alanine, threonine, leucine, or α -hydroxymethylserine.

401. The peptide dimer of Claim 400 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

402. The peptide dimer of Claim 394 wherein at least one amino acid of P₁ other than β -alanine, when present, is a D-amino acid.

403. The peptide dimer of Claim 394 wherein all of the amino acids of P₁ other than β -alanine, when present, are D-amino acids.

404. The peptide dimer of Claim 394 wherein both P₃ peptides are P₁.

405. The peptide dimer of Claim 392 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₃ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

406. The peptide dimer of Claim 392 wherein P₃ comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P₃.

407. The peptide dimer of Claim 392 wherein L is neutral.

408. The peptide dimer of Claim 392 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

409. The peptide dimer of Claim 408 wherein L contains 2-8 carbon atoms.

410. The peptide dimer of Claim 392 wherein L is a cyclic alkane residue containing from 3-8 carbon atoms.

411. The peptide dimer of Claim 410 wherein L contains 3-5 carbon atoms.

412. The peptide dimer of Claim 392 wherein L is a nitrogen-containing heterocyclic alkane residue.

413. The peptide dimer of Claim 412 wherein L is a piperazide.

414. The peptide dimer of Claim 392 wherein L is a glyceryl ester.

415. A method of *in vitro* fertilization wherein a medium is utilized which comprises an amount of a peptide effective to reduce the damage done by reactive oxygen species, the peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

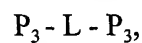
n is 0-100;

or a physiologically-acceptable salt thereof.

416. The method of Claim 415 wherein at least one amino acid of P_1 , at least one amino acid of P_2 , or both is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

417. A method of *in vitro* fertilization wherein a medium is utilized which comprises an amount of a metal-binding peptide effective to reduce the damage done by reactive oxygen species, the metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

418. A method of *in vitro* fertilization wherein a medium is utilized which comprises an amount of a metal-binding peptide dimer effective to reduce the damage done by reactive oxygen species, the peptide dimer having the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.